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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/402,732 | 12/01/1999 | ALVIN H. SCHMAIER | 8820-3 | 6339 |

23973 7590 01/29/2004

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| EXAMINER | |
|---|---|
| GUPTA, ANISH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1654 | |

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/402,732 | SCHMAIER ET AL. | |
| | Examiner | Art Unit | |
| | Anish Gupta | 1654 | |

*-- The MAILING DATE of this communication app ars on the cover sheet with the correspondenc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election with traverse of Group II, claims 1-25 is acknowledged. To further prosecution, Group I and II have been combined and examined in their entirety. Group III remains restricted. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement to Group III, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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1. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. § 112, second paragraph by providing clear warning to others as to what constitutes infringement of the patent. See *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). If

the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. § 112, second paragraph would be appropriate. See *Morton Int'l, Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

Here, the claim recites that peptides are effective in inhibiting "other cell activation." However, it is unclear what activations would qualify as "other cell activation" within the meaning of the claim. It is unclear if cell activation can be defined as any response to stimuli or just thrombin induced stimuli. Thus, one of ordinary skill in the art cannot interpret the metes and bound of the claim.

The claim recite that X1 is "from zero to thirty amino acids from amino acids 1-30 of SEQ ID NO: 1" It is unclear from the claim if the zero to thirty amino acids are inclusive of specific fragments or are any amino acids from SEQ ID NO: 1. That is, say X1 is a pentapeptide. Must this pentapeptide be chose from a specific pentapeptdie fragment from 1-30 of SEQ ID NO:1 or can it be chosen from random amino acids within the 1-30 Sequence.

The claims state that the compounds have segments that are "different." It is unclear how the segments can be different. Note that X1 and X2 are specifically defined in base claim and are required to be the same in the branched peptides. For example, in the sequence L-($X_1$-Arg-Pro-Pro-$X_2$)$_n$ if X1 and X2 are allowed to be Ala, then regardless of what n is defined as, the sequence will remain Ala-Pro-Pro-Ala in all of the "segments" or branches. Thus, the branched amino acids will be identical rather than different.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-25 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the analogs of SEQ ID 6, SEQ ID 7, the peptide RPP, the peptide RPP MAP-4 and the peptide RPP heterodimer for inhibiting thrombin induced platelet aggregation, does not reasonably provide enablement for all of the compounds claimed in the claims and inhibition of "other cell activation." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

*(1) The nature of the invention:*

The claims are drawn to a method of inhibiting thrombin-induced platelet or other cell activation by administering peptides having the minimum sequence -Arg-Pro-Pro-Gly-.

*(2) The state of the prior art*

The art has recognized peptides comprising the above amino acid sequences that inhibiting thrombin induced platelet activation and cell activation. However, the art has also recognized peptides having bradykinin fragments or analogs thereof, are not effective in inhibiting platelet activation or other cell activation. For example, the reference of Hasan et al. (applicants work) clearly state that bradykinin and its analogs did not inhibit ADP-induced platelet activation (see abstract), collagen activation, U46619 platelet activation. The reference concludes that bradykinin analogs comprising sequence RPPGF are selective inhibitors of platelet activation.

As with all peptides, activity is based on the 3-dimensional structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the peptide to be active. It is known in the art that the three dimensional structure of the peptide cannot be based on structure alone. For example, in peptide chemistry Ngo et al. teach that for proteins and peptides, a " 'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from its amino acid alone (see page 492 in Ngo et al.). Thus, activity of a given peptide can not be based on its structure alone. Similarly, the Rudinger article (see the conclusions in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

*(3) The relative skill of those in the art*

The relative skill of the those in the art is high.

*(4) The predictability or unpredictability of the art*

The unpredictability of the peptide art is very high. The true fact of the state of the art in peptide chemistry is expressed succinctly in the Rudinger article (see the conclusions in particular). "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

*(5) The breadth of the claims*

The breath of claims is very broad. The claims allow for any substitution up to 30 amino acids at the N-terminus and C-terminus of the RPP sequence which are all effective in inhibiting ADP-induced platelet aggregation, ADP-induced platelet activation and other cell activation. Further, the claims allow for branched peptides that have up to 20 similar or different branches.

*(6) The amount of direction or guidance presented and (7) The presence or absence of working examples*

As stated above, the art recognizes that not all peptide containing the sequence RPP sequences are effective in inhibiting platelet activation. Hansan et al. states that RPPG containing peptides did not inhibit ADP-induced platelet activation. It is acknowledged that the claim specifically recite that in X1-Arg-Pro-Pro-X2, the X2 cannot contain a glycine residue in the N-terminal. However, given the similarity of the claimed peptides and those disclosed in the prior art one would conclude that the activity attributed to the RPPG containing sequences would also be observed in RPP containing sequence. Applicants' specification has not provided any evidence to rebuff this proposition. The specification does not contain any example that would demonstrate that RPP containing sequence would be effective in inhibiting ADP-platelet cell activation or "other

cell" activation. Rather, the specification discusses at great length, similar to Hansan et al., the effectiveness of RPPG containing peptides in inhibiting thrombin induced platelet activation. Therefore it would be unpredictable to determine the ADP-platelet inhibitory activation or cell activation activity any peptide having the sequence RPP.

Moreover, this teaching also complicates the use of peptides having up to 30 amino acids on the C- and N- terminus. The specification does not proved guidance of peptides having up to 30 amino acids on the N- and C- terminus or branched amino acid sequences that would be effective in inhibiting platelet activation of any type. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. Here, the art has recognized that modification in the amino acid sequences can lead to dramatic effects, see Ngo et al. and Rudinger et al. Applicants specification does not provide any examples that would demonstrate that peptides five or six amino acids are effective in inhibiting. Since one does not know how a protein will fold and since one does not know the effect of a single replacement of an amino acid, one cannot readily determine the effectiveness of the peptides in the inhibition of cell activation. As

further evidence of this proposition, attention is directed to Hansan et al. In Hansan, it was demonstrated that the peptide RPPGF produced inhibition of thrombin induced platelet aggregation. However, scrambled peptides of RPPGF or peptide of the sequence PPGFSP where R was deleted and FSP were added, produced very poor results (see page 519-520). Thus, addition and/or deletions have dramatic effects in activity.

*(8) The quantity of experimentation necessary*

In conclusion, since the significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine the all of the peptide analogues would not affect the property of the peptide.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can normally be reached on (703)308-2923. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

1/24/04

Anish Gupta